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TOPOLOGICAL INDICES AS CHEMICAL BEHAVIOR DESCRIPTORS(U)
GEORGIA UNIV ATHENS DEPT OF CHEMISTRY D H ROUVRAY
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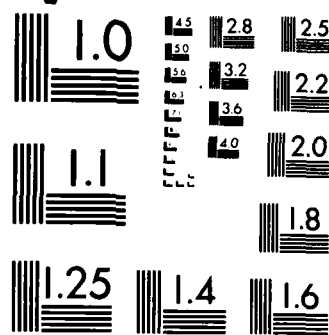
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by

D.H. Rouvray

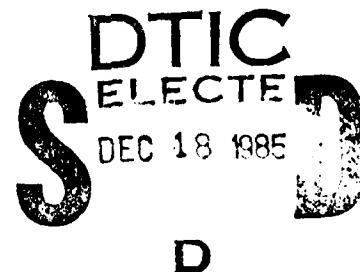
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TOPOLOGICAL INDICES AS CHEMICAL BEHAVIOR DESCRIPTORS

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Abstract

Graph theorists have contributed steadily to the development of chemistry since the pioneering work of Arthur Cayley on isomer enumeration in the mid-1870s. Their contributions, however, have been confined mainly to one or two applications only. After briefly reviewing the principal applications of graph theory and combinatorics in chemistry, it is pointed out that there are still numerous interesting mathematical problems waiting to be tackled. A number of these involve the various graph invariants used by chemists to characterize molecular graphs; in this context such invariants are usually referred to as topological indices (TIs). Many different TIs have been put forward to date and most have been employed to characterize chemical behavior dependent upon either (a) molecular size, (b) molecular shape, or (c) specific molecular sites within a molecule. Three comparatively simple TIs based on the distance matrix are exhibited. The first of these has been used to predict the physicochemical properties of hydrocarbon molecules; the second, properties which depend on the degree of branching present in molecules (such as the octane number of fuels); and the third, the occurrence of carcinogenicity, mutagenicity or teratogenicity in polycyclic aromatic species (polyhexes). Current work on TIs and some of the mathematical problems associated with their further development are briefly outlined. The paper is presented primarily to encourage interested mathematicians to take a closer look at the chemical applications of graph theory.

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Introduction

The manifold interactions of graph theory with chemistry at the present time by no means represent a recent phenomenon. The first such interaction occurred over a century ago when Cayley(1) devised a method for enumerating the isomers of several series of molecules having tree graphs. Since his time, many mathematicians have made notable contributions to chemistry and cross-fertilization between the two disciplines has become increasingly evident. In Table 1 we list several of the mathematicians who have worked on chemical problems; their names had to be selected arbitrarily, for a list which included all such contributions would quickly exceed manageable proportions. Over the years, a number of graph theorists have acknowledged their indebtedness to chemical ideas as a source of inspiration. Thus, Sylvester(2) was able to write "I hardly ever take up Dr. Frankland's exceedingly valuable 'Notes for Chemical Students' without deriving suggestions for new researches in the theory of algebraical forms."

Many of the textbooks on graph theory have made mention of chemical applications. Among these are the first book on the subject by Konig(3), the well-known text by Harary(4), and a monograph on graph spectral theory by Cvetković, Doob and Sachs(5). In fact, the latter work contains a fair number of results obtained by chemists who have applied graph theory in the area of bonding theory. An exposition of the history of graph theory to 1936 by Biggs, Lloyd and Wilson(6) devotes a whole chapter to a discussion of some of the more important interactions between chemists and graph theorists which have taken place since the mid-1870s.

Although it is not widely known, the word 'graph' itself is of chemical origin. The term was first suggested by Sylvester(2), who felt that it would provide a convenient abbreviation for the 'graphical notation' of the chemists of his time. The word thus initially referred to the representation of molecular species by means of structural formulas. In chemistry itself, graphs were first employed at a very early stage of development of the discipline. Their use can certainly be traced back to 1759, when Cullen(7) introduced so-called 'affinity diagrams' to represent the forces existing between pairs of interacting

| Mathematician | Year | Application to chemistry |
|------------------|------|--|
| Arthur Cayley | 1874 | Isomer enumeration - trees |
| William Clifford | 1875 | Matrices for atomic structures |
| James Sylvester | 1878 | Graphical representation of molecules; first use of the term 'graph' from the chemists' 'graphical notation' |
| Arthur Lunn | 1929 | Isomer enumeration |
| Dénes König | 1936 | First book on graph theory - with several chemical references |
| George Pólya | 1937 | Enumeration Theorem - application to isomer enumeration |
| Charles Coulson | 1940 | Bonding theory; Pairing Theorem |
| Frank Harary | 1969 | Textbook on graph theory - with chemical references; work on isomer enumeration and chemical documentation |
| Allen Schwenk | 1974 | Chemical bonding theory |
| Robert Robinson | 1976 | Isomer enumeration |
| George Hall | 1977 | Chemical bonding theory |
| Ronald Read | 1978 | Chemical documentation |
| Dragoš Cvetković | 1980 | First book on graph spectra - with many references to chemical work, especially bonding theory |
| Michael Doob | | |
| Horst Sachs | | |

Table 1. Some mathematicians who have applied graph theory to chemistry

chemical species. The first application of graphs for the depiction of individual molecules, however, was made in 1789 by Higgins(8). Another word which has its origins in chemical terminology is valence. Terms widely used nowadays with the same meaning in both disciplines include: cycle index, cyclic, distance matrix, eigenvalue, enumeration, and polyhedron.

Over the years, applications of graph theory to chemistry have tended to come in waves, with periods of great activity followed by intervals of relative calm. The episodic nature of the development of the field is evidenced by major surges of activity in the 1870s (Cayley, Sylvester), the 1930s (Senior, Pólya), and in the 1970s (Balaban, Harary). The peaks of activity thus seem to have occurred in roughly 50 year cycles. The current surge, which began to manifest itself at the beginning of the 1970s, has continued to grow up the present time. It shows no sign of abating, as will be apparent from Figure 1, which presents a plot of the number of papers appearing annually in applications of graph theory to chemistry for the years 1972-1984. There has been a more or less steady increase of 25% per annum in the number of papers over this period, and the current annual output is now rapidly approaching 500.

The Principal Applications

Although there are numerous applications of graph theory to all the various branches of chemistry, the principal applications to date can be subdivided into eight major categories. These eight categories are listed in Table 2, together with a brief indication of the type of mathematics involved. More details on the different applications can be found in a number of general reviews of the field (9-13).

The oldest applications of graph theory to chemistry are in the areas of chemical documentation and isomer enumeration. As mentioned above(8), the first application in chemical documentation can be traced back to 1789. Since that time, numerous workers have attempted to represent and classify all the contemporary known chemical compounds. As this number currently stands at over 7 million different compounds, the task of uniquely characterizing all of them is clearly a major

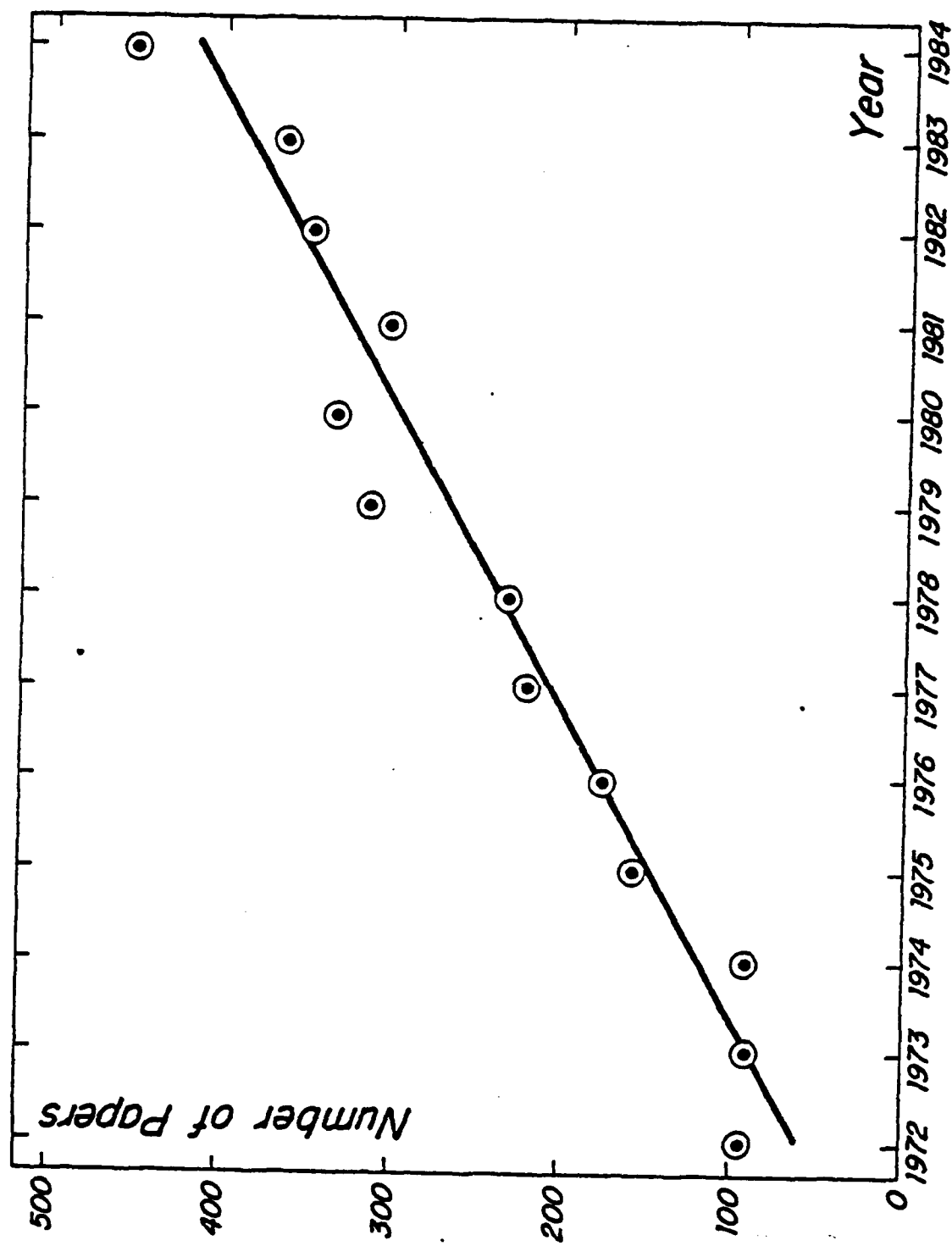


Figure 1. Plot of the annual number of papers published on the chemical applications of graph theory

| Area of Application | Essential Mathematics Involved |
|--|--|
| <p>Chemical Documentation</p> <p>Isomer Enumeration</p> <p>Additive Properties</p> <p>Bonding Theory</p> <p>Chemical Reactions</p> <p>Synthesis Routes</p> <p>Macromolecules and Polymers</p> <p>Topological Indices</p> | <p>Representation, classification and enumeration of molecules by chemical graphs</p> <p>Study of the permutation groups of graphs</p> <p>Linear combinations of graph-theoretical invariants</p> <p>Graph spectral theory</p> <p>Representation by reaction graphs and group theory</p> <p>Network theory and combinatorics</p> <p>Graph theory and combinatorics</p> <p>Correlations using individual graph-theoretical invariants</p> |

Table 2. The principal applications of graph theory in chemistry with an indication of the specific area of mathematics involved in each case

one. Progress in this field has recently been reviewed by Goodson (14). The closely associated area of isomer enumeration is probably the best known application among mathematicians. From its inception in 1874 by Cayley(1), the field received its most important boost in the years 1936-1937 when Pólya(15) published his now famous Enumeration Theorem and applied it to the enumeration of a variety of different chemical compounds. Developments in the field up to 1974 have been comprehensively reviewed by Rouvray(16). Because so much has been accomplished in this now very well-established area, there is comparatively little remaining to be done. Accordingly, it is recommended that interested mathematicians avoid entering this particular field.

Additive properties of molecules are those which may be calculated simply by summing the contributions to the property by the component parts of the molecule. Thus, if a molecule is expanded by the addition of an extra constituent, such as a methylene(CH_2) group, there will be some constant increase in the additive property for each group added. Series of molecules formed in this way whose members differ by a methylene group are referred to by chemists as homologous series. Probably the best known homologous series is the alkane series, whose members are as follows:

| | | | | | | |
|---------------|------------------------|------------------------|---------------------------|---------------------------|-------|-----------------------------|
| CH_4 | C_2H_6 | C_3H_8 | C_4H_{10} | C_5H_{12} | | $\text{C}_n\text{H}_{2n+2}$ |
| methane | ethane | propane | butane | pentane | | general alkane |

In all homologous series (and in many others) there exists approximate transferability of the force constants for bonds of the same type from molecule to molecule, i.e. the C-H bond in methane has closely similar properties to that in pentane and may be used to substitute for it in calculations. Whenever such additivity holds, the physicochemical properties of molecules can be represented as linear combinations of graph-theoretical invariants, as pointed out by Gordon and Kennedy(17). This same reasoning also provides the theoretical underpinning for the utilization of topological indices, a topic we return to below.

The application of graph theory to the study of chemical bonding has proven to be an extremely fruitful area of research which has afforded many new insights. In essence, the field involves graph spec-

tral theory, for the eigenvalues of the adjacency matrices used to represent molecules yield the energy levels of those molecules(18). Since the distribution and electron occupancy of the energy levels in molecules basically determines the chemical behavior of species, the importance of spectral theory to the chemist can hardly be exaggerated. A number of the theorems developed by chemists working in this area appear in the book by Cvetković et al.(5). Many of the important results obtained in this area are due to Trinajstić(19) and his associates in Yugoslavia.

In applying graph theory to the study of chemical reactions, vertices usually represent entire chemical species and edges chemical processes. The chemical process may entail the breaking of chemical bonds or transformations, such as rotations, which do not involve bond breaking. The design of synthesis routes starting from a set of molecules, called synthons, involves the stepwise assembly of small molecules leading to the eventual synthesis of some very complicated end product. The various stages of the synthesis can be represented by a so-called reaction graph giving all the conceivable synthetic pathways. In the synthesis of macromolecules and polymers, we consider the various sites and modes of attachment of other molecules to the starting monomers. This process of attachment may be one of polymerization or polycondensation and results in the formation of dimers, linear polymers, or cross-linked polymers. Such polymeric species display a number of interesting properties, some of which can be explored using graph theory. For further information on these applications, the reader is referred to the review by Rouvray and Balaban(11).

Topological Indices

We turn now to a rather more detailed discussion of topological indices, an area of application of graph theory which has recently become of considerable importance in chemistry. Topological indices (TIs) are simply graph invariants which are employed for the purpose of characterizing the properties of molecules which form homologous or other chemical series. In purely chemical language, a TI is usually described as a scalar descriptor used to express numerically the neighborhood relations existing within a chemical graph. Such an index

is obtained by applying some mathematical algorithm to the whole or part of the chemical graph. (It should be mentioned in passing that the chemical graphs used in this context represent all of the atoms in the molecule except the hydrogen atoms, which are not structure-determining; these graphs are thus more correctly referred to as hydrogen-suppressed chemical graphs.) The resulting characterizations are not unique - at least none has so far been demonstrated to be unique - though for the restricted classes of graphs of interest to chemists the non-uniqueness is not a major problem. Over the past few years, several attempts have been made(20) to derive TIs which approach uniqueness in their characterization of tree graphs, a class of great importance to the chemist.

To date, around 50 different TIs have been put forward in the chemical literature. These have recently been reviewed by Balaban et al.(21), Bonchev(22), and Rouvray(23). Because TIs provide the chemist with a convenient mathematical description of chemical structure, comparison of different structures becomes effectively a comparison of mathematical invariants representing the structures. On the basis of some postulated structure-activity relationship, such comparisons can provide valuable information on which structural components of molecules are dominant for the property of interest. Most of the TIs proposed up to the present may be derived either from the adjacency matrix or distance matrix of the chemical graph. To illustrate now some of the ways in which TIs have been used by chemists, we exhibit three such indices, all of which derive from the distance matrix. The derivation of each of these indices is schematically depicted in Figure 2 for the molecule of normal butane, C_4H_{10} .

The Wiener Index

The first TI was published as long ago as 1947 by Wiener(24) for the purpose of characterizing alkane species. It has proved to be so useful that it is still widely employed today. The index may be defined as the total number of bonds(edges) traversed in moving from a given atom(vertex) to each of the other atoms(vertices) in the structure. The index is thus equal to one half the sum of the elements in the distance matrix for the chemical graph:

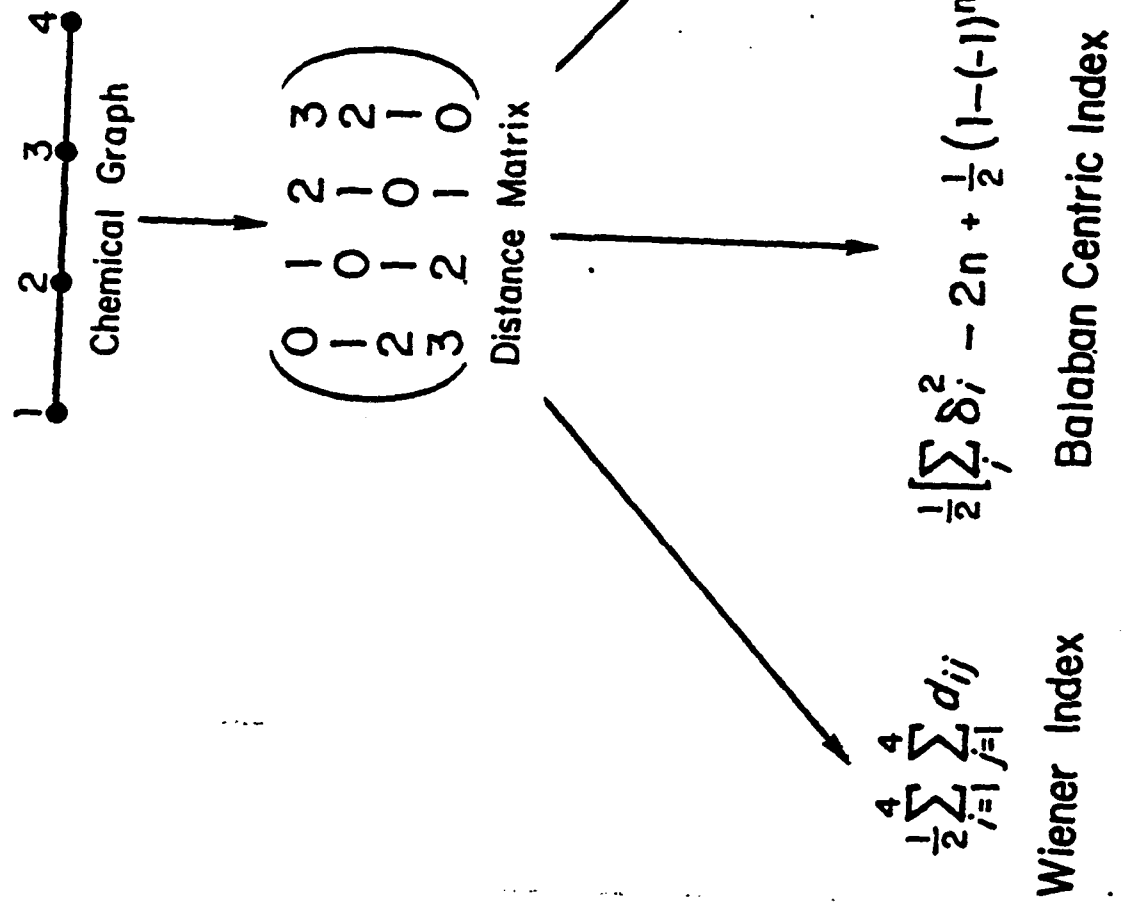


Figure 2. Schematic representation of three topological indices from the distance matrix of n-butane

$$W(G) = \frac{1}{2} \sum_{i=1}^n \sum_{j=1}^n d_{ij}$$

where n is the number of atoms in the chemical graph, i.e. all atoms are included in the count except the hydrogen atoms. The index is known to provide a fairly accurate measure of the volume of space occupied by a molecule, i.e. of molecular size. It is thus extremely useful for correlating and predicting physicochemical properties which are determined by the size of the molecules constituting the bulk phase.

Examples of properties which are dependent upon molecular size are the additive physicochemical properties referred to earlier. This is only to be expected, for such properties are known to increase in a regular fashion with increasing molecular size. Properties which satisfy this criterion include the melting point, boiling point, refractive index, density, surface tension, viscosity, molar volume, and heats of formation and vaporization. There is thus a large number of parameters which can be correlated against the Wiener index. Actual studies carried out on the members of homologous and other series have in all cases yielded good to excellent correlations(25).

The Balaban Centric Index

This index was derived by Balaban(26) in 1979 with the aim of characterizing the amount of branching present in molecules possessing tree graphs. The normalized centric index can be defined in symbols in the following way:

$$B(G) = \frac{1}{2} \left[\sum_1 \delta_1^2 - 2n + \frac{1}{2} (1 - (-1)^n) \right]$$

and is comprised of two basic parts. The first part, the summation $\sum_1 \delta_1^2$, is the centric index proper and is defined in terms of a pruning sequence on the tree. In the first step we imagine all vertices of degree one and their incident edges to be removed from the tree. Let us suppose that δ_1 vertices are pruned away in this step. The process is then continued in the same way to yield δ_2 for step two, δ_3 for step three, and so on until all of the n vertices have been excised. The sum of the δ_i^2 over all i steps gives us the centric index, $B'(G)$.

The second part of $B(G)$, which assumes the form $(2n - \frac{1}{2}[1-(-1)^n])$, is simply the value of $B'(G)$ for the straight chain molecule with n atoms (the unbranched path on n vertices). By subtracting the second part from the first part, we obtain a measure of the amount of branching present in the molecule. The factor $\frac{1}{2}$ appears in the expression for $B(G)$ to ensure that the lower bound for the chain molecule (path graph) will be precisely zero.

Since this index was designed specifically to provide a measure of the branching present in molecular species, it reflects the mode of distribution of the volume of a molecule in space, i.e. it is closely related to molecular shape. The index is thus employed whenever branching is of importance in determining some physicochemical property. One example of a property of this type is the octane number of fuels such as gasoline. The octane number offers a reliable indication of the anti-knock characteristics of the fuel in question. In general, the more branched the fuel molecules are, the less likely they will be to self-ignite or 'knock' upon sudden compression in air. Balaban and Motoc (27) calculated the normalized centric indices for the isomeric heptanes (C_7H_{16}) and the octanes (C_8H_{18}) and obtained very good correlations with their octane numbers. This work demonstrated conclusively that the anti-knock behavior of alkane species increases with both an increasing amount of branching and with a decreasing number, n , of carbon atoms in the molecule.

The Seybold Atomic Index

Although this particular index was originally introduced by Bonchev and Balaban (28) in the form of a code for all the atoms in a molecule, it was first applied to the study of the individual atoms by Seybold (29). The molecules he studied were polycyclic aromatic hydrocarbons which have graphs in the form of polyhexes. This index was designed for the purpose of eliciting information about a given region or site within a molecule rather than characterizing the molecule as a whole. It is thus very valuable for providing information about a single atom or a small group of atoms in a molecule. The index is defined in the following way:

$$S(G) = \sum_{j=1}^n d_{ij}$$

and thus represents the sum of the shortest paths from vertex i to every other vertex in the graph. The index for the i th atom may be obtained by summing the d_{ij} elements in the distance matrix either along the i th row or down the i th column. Because this index yields a measure of the connectivity of each atom in a molecule, it is especially useful in the study of electron flows within molecules.

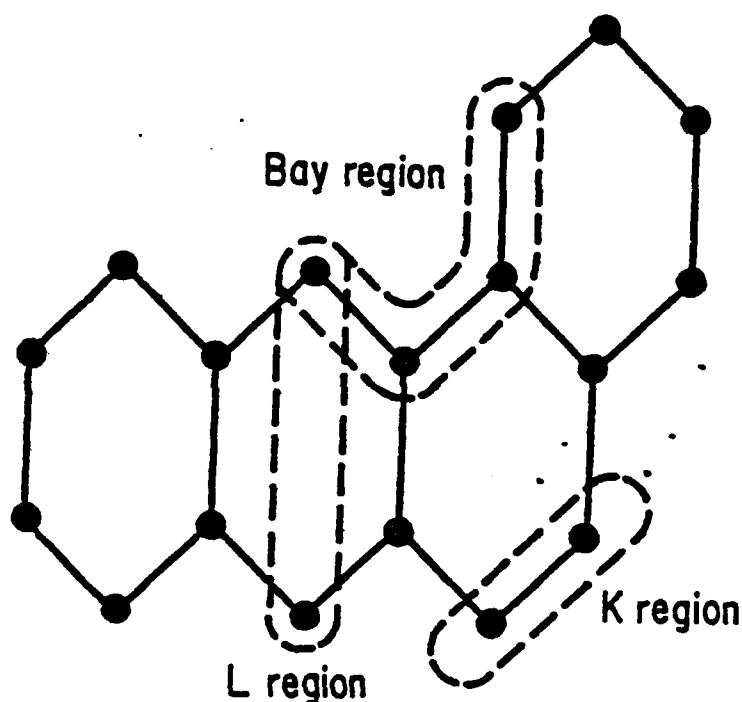


Figure 3. Special regions in the chemical graph of benz[a]anthracene

Phenomena which depend on specific regions or sites in molecules are frequently encountered in the realms of biochemistry, pharmacology, physiology, and toxicology. Among the very broad variety of phenomena of this type, mention may be made of carcinogenesis, mutagenesis, and teratogenesis. In such phenomena, one or two comparatively small regions of the molecule concerned play a crucial role, either because they are especially active or inactive, or because they are able to fit into some appropriate biological receptor within living organisms. The rest of the molecule is often of relatively minor importance.

Polycyclic aromatic hydrocarbon molecules are well known to have regions which are of prime importance in determining whether or not they exhibit carcinogenic behavior. These regions of importance are illustrated in Figure 3. The K region behaves like an 'on' switch when the activity of the atoms reaches a certain level; the L region acts like an 'off' switch; and the bay region facilitates the formation of reactive intermediates. By using his index to characterize the atoms in each of these three regions, Seybold(29) was able to predict which molecules would behave as carcinogens in experimental animals and also obtain reliable correlations on the degree of carcinogenicity exhibited by such molecules.

Some Graph-Theoretical Problems

To date, around 50 different TIs have been postulated in the chemical literature and most of them have been applied in one or more of the various branches of chemistry. Since TIs are just graph invariants, it should not come as a surprise that a large number of problems of a purely graph-theoretical nature have arisen as a result of applying these indices. As many of the problems are non-trivial and of potential interest to graph theorists, we list below several of the more urgent problems currently waiting to be tackled. The most effective way of investigating problems of this type may well involve collaborative endeavors between mathematicians and chemists. Here, in mathematical language, are some of the major problems:

1. If we take 50 as the number of TIs currently available to chemists, there will be $\binom{50}{2} = 1,225$ different relationships between pairs of TIs which need to be examined. A compilation of TIs, similar to that of Brigham and Dutton(30) on relations between various graph invariants, would seem to be called for. Understanding the interrelationships between all the TIs is of considerable interest to chemists at present, especially knowing which TIs are closely related, which yield essentially the same information about a graph, and which are redundant.
2. The occurrence of the same value of a given TI for different graphs, and indeed the whole question of the uniqueness of the characterizations provided by TIs, needs to be addressed. Several interesting

questions present themselves. Among these are: (i) does any TI known at present offer a unique characterization?; (ii) can TIs be developed which uniquely characterize graphs?; and (iii) if the answer to (ii) is negative, can such TIs be derived for restricted classes of graphs of especial interest to chemists, e.g. trees and polycyclic graphs?

3. The calculation of TIs, especially for cyclic species, is often tedious and can present problems. The development of recurrence relations for each of the indices would greatly facilitate their calculation and enable appropriate algorithms and computer programs to be written.
4. It would be very interesting to know which of the TIs are ultimately derivable from either the adjacency matrix or the distance matrix of the chemical graph. In some instances, this is immediately obvious, e.g. in the case of the Wiener index, but in other cases it poses a non-trivial problem.
5. As explained earlier, the eigenvalues of the adjacency matrix of the chemical graph are known to yield the energy levels of the molecules concerned. The eigenvalues of the distance matrix have, however, not been examined for possible chemical significance. In general, the role of the eigenvalues of chemical graphs requires considerable further study.
6. The treatment of branching in chemical species has presented numerous problems. The fundamental problem here is that there is no reliable measure of the amount of branching present in graphs of chemical interest. In spite of several attempts by chemists(31) to overcome this problem, there is still some uncertainty as to the best way of dealing with branching. Moreover, since correlations with physicochemical properties for branched species are in general not as good as those for unbranched species, the question arises: can indices be developed which offer an effective means of correlating the branched species?
7. Some method of deciding which TIs provide a measure of the branching present in the chemical graph and which merely reflect the overall size of the graph would be valuable to the chemist. It may even be possible to order indices according to the extent to which they

mirror molecular size versus molecular shape. A suitable technique for incorporating in TIs the amount of bending in a chemical graph, e.g. in polyhex graphs, could also have several advantages.

8. A related issue involves the development of a scheme for deciding a priori which indices will be effective for a specific role. Thus, if a given physicochemical property is known to be $\alpha\%$ determined by molecular size and $\beta\%$ by molecular shape, can algorithms be written which could use this information to construct an optimized TI for the characterization in question? Alternatively, if a reliable characterization is attained, can a simple procedure be developed for calculating α and β ?

Conclusion

We have attempted to outline the principal applications of graph theory which have been made in chemistry up to the present time. Special attention has been focused on the specific area of topological indices because of its current importance. Several of the problems associated with the further development of this field have been delineated. It is hoped that this paper may serve to stimulate mathematicians to consider entering - probably jointly with chemists - the interdisciplinary area of chemical applications of graph theory. In this way it is anticipated that not only will the field of chemistry be considerably enriched but that mathematicians will become increasingly aware of the important contributions they have made to chemistry in the past and, we may hope, will continue to make to an increasing extent in the future.

It would seem appropriate to end our paper with two further quotes from the mathematician James Sylvester. In 1878, Sylvester(2) made a prefatory remark concerning his first paper on chemical applications of graph theory which might well be applied as a suitable epithet to our own little contribution: "This paper may at worst serve to suggest to chemists and algebraists that they may have something to learn from each other." In the same year he also commented (2) that: "There is a wealth of untapped mathematical potential contained in the patient and long investigations of our chemist fellows." These words ring no less true today than when they were written over a century ago.

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